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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re U.S. Patent No. 4,284,647

Issued: August 18, 1981

To: Saul W. BRUSILOW, Mark L. BATSHAW and Norman S. RADIN

For: PROCESS FOR WASTE NITROGEN REMOVAL

* * * * *

February 22, 1988

APPLICATION FOR EXTENSION OF PATENT TERM UNDER § 156

Hon. Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

THE JOHNS HOPKINS UNIVERSITY a corporation of the State of Maryland, located at Baltimore, Maryland (hereinafter "Applicant"), is the owner of the entire interest in and to Letters Patent of U.S. Patent No. 4,284,647 (hereinafter "the Patent") granted to Saul W. Brusilow, Mark L. Batshaw, and Norman S. Radin for PROCESS FOR WASTE NITROGEN REMOVAL by reason of an assignment to Applicant recorded in the United States Patent and Trademark Office on June 17, 1980 at Reel 3770, Frames 773-775, and corrected assignment to Applicant recorded June 16, 1981 at Reel 3863, Frame 142-143. KENDALL-McGAW Laboratories, Inc., of Santa Ana, California (hereinafter "Kendall-McGaw") has been authorized by Applicant to, inter alia, utilize and authorize others to utilize the process invention claimed in the Patent, and to file for and obtain FDA approval for such use.

Applicant, through undersigned counsel, hereby applies for a two year extension of the term of United States Patent No. 4,284,647 under 35 U.S.C. 156 on the basis of the following information submitted in accordance with the provisions of Title 37 C.F.R. section 1.740(a)(1)-(17), set forth in the sequence of those subparagraphs. Filed herewith is a Power of Attorney authorizing the undersigned to prosecute this Application for Extension of Patent Term, and to transact all business in the Patent and Trademark Office and the Department of Health and Human Services in relation thereto.

(1) This application for extension is based upon the regulatory review period before the Food and Drug Administration ("FDA") of Kendall-McGaw's approved product "Ucephan", indicated for some types of urea-cycle enzymopathies. "Ucephan" is an oral solution of sodium salts of benzoic acid and phenylacetic acid, as more particularly described in the package insert attached hereto as EXHIBIT 1, which was approved by the FDA as a part of NDA 19-530 (more fully identified below).

(2) The approved product was subject to regulatory review under Federal Food, Drug and Cosmetic Act, Section 505 (21 U.S.C. 355).

(3) The approved product "Ucephan" received permission for commercial marketing or use after a regulatory review period under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on December 23, 1987.

(4) The active ingredients in the approved product, "Ucephan", are sodium benzoate and sodium phenylacetate, each of which are present in the amount of 10% in an oral solution. To the best of applicant's knowledge, the permission for the commercial marketing or use of this product after such regulatory review period is the first permitted commercial marketing or use of the "product" (as that term is understood by applicant to be used in 35 U.S.C. §156(a)(5)(A)) for the approved composition and indicated use under the Federal Food, Drug and Cosmetic Act. Applicant is presently without sufficient information upon which to state whether or not, or when, others may have previously obtained approval for commercial marketing or use under the Federal Food, Drug and Cosmetic Act of other products which may contain one or more of the above active ingredients in compositions, and for indications, different from that of the approved product under NDA 19-530.

(5) This application for extension of patent term under 35 U.S.C. 156 is being submitted within the permitted 60 day period, which period will expire on February 22, 1988.

(6) The patent for which an extension is being sought is as follows:

U.S. Patent No. 4,284,647

Issued: August 18, 1981

Inventors: Saul W. Brusilow
Mark L. Batshaw
Norman S. Radin

(7) A copy of the patent for which an extension is being sought, including the entire specification, claims and drawings, is attached as EXHIBIT 2.

(8) There is no disclaimer, certificate of correction or reexamination certificate in the subject patent, and it is not subject to maintenance fee payments.

(9) U.S. Patent No. 4,284,647, for which this extension is sought, generally claims a process for controlling waste nitrogen accumulation diseases in humans, caused by an impairment in the normal synthesis of urea from ordinary waste nitrogen or in the normal excretion thereof, by the administration of benzoic acid, phenylacetic acid and/or non-toxic pharmaceutically-acceptable salts of such acids, to a human suffering from such waste nitrogen accumulation disease. The approved product is an oral solution of sodium benzoate and sodium phenylacetate indicated for treatment of certain urea-cycle enzymopathies, and is covered by claims 1, 4, 8 and 9, as described in more detail below:

> Claim 1 A process for controlling waste nitrogen accumulation diseases in humans, caused by an impairment in the normal synthesis of urea from ordinary waste nitrogen in the body or in the normal excretion thereof, said process comprising administering an effective amount of at least one compound selected from the group consisting of benzoic acid, phenylacetic acid and the non-toxic, pharmaceutically-acceptable salts of said acids to a human suffering from such waste nitrogen accumulation disease, the amount of said compound used being sufficient to react with the waste nitrogen to form an amino acid acylation product for urinary discharge of said product.

The approved product is an oral solution of sodium benzoate and sodium phenylacetate administered to humans to control certain urea cycle enzymopathies, a type of waste

nitrogen accumulation disease. As described in the approved package insert (EXHIBIT 1), the mechanisms involved are conjugation reactions involving acylation of amino acids, and excretion of the conjugation product.

> Claim 4 The process of claim 1 wherein the human is one with a urea-cycle enzymopathy.

As described under "Indications and Usage" in the approved package insert (EXHIBIT 1), the approved product is administered to humans to control certain urea-cycle enzymopathies.

> Claim 8 The process of claim 1 wherein the administration of the benzoic acid or phenylacetic acid, or salts thereof, synthesizes hippuric acid and phenylacetylglutamine, respectively, and the synthesized product is discharged as urinary nitrogen.

As described under "Clinical Pharmacology" in the approved package insert (EXHIBIT 1), following administration of the approved product, the benzoate conjugates with glycine to form hippurate, and phenylacetate conjugates with glutamine to form phenylacetylglutamine. The synthesized product is discharged as urinary nitrogen.

> Claim 9 The process of claim 1 wherein the salt is sodium salt.

The approved product involves the administration of an oral solution of **sodium** benzoate and **sodium** phenylacetate.

(10) The relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) Issue date of patent: August 18, 1981;

(b) Effective date of IND applications:

IND 17,123 for Sodium Phenylacetate obtained January 10, 1980;

IND 17,336 for Sodium Benzoate obtained on March 17, 1980;

(c) NDA 19-530 for Ucephan initially submitted September 30, 1985;

(d) NDA 19-530 for Ucephan approved on December 23, 1987.

(11) A brief description of the significant activities undertaken by or on behalf of the marketing applicant during the applicable regulatory review period with respect to the approved product, and the significant dates applicable to such activities, are set out in EXHIBIT 3.

(12) Applicant is of the opinion that U.S. Patent 4,284,647 is eligible for extension under 35 U.S.C. 156 because it satisfies all the requirements for such extension inasmuch as:

(i) such patent claims a method of using a product (35 U.S.C. 156(a);

(ii) the term of such patent has not expired before submission of this application (35 U.S.C. 156(b);

(iii) the term of such patent has never been extended,

(iv) the application for extension is submitted by the owner of record, through undersigned counsel, in accordance with the requirements of 35 U.S.C. 156(d);

(v) the approved product, "Ucephan", has been subject to a regulatory review period before its commercial marketing or use; and

(vi) the permission for the commercial marketing or use of the product, "Ucephan", after the regulatory review period, is the first permitted commercial marketing or use of the approved product under the provisions of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) under which such regulatory review period occurred.

Applicant requests an extension of the patent term of U.S. Patent No. 4,284,647 by two years. Inasmuch as such patent issued

before September 24, 1984, and a request (IND) was submitted for an exemption under subsection (i) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) before September 24, 1984, and the commercial marketing or use of the product was not approved before September 24, 1984, the maximum extension available under 37 C.F.R § 1.775(d)(6)(ii) is two years. Since the time between the filing of the NDA 19-530 for "Ucephan" on September 30, 1985 and its approval on December 23, 1987 is already in excess of two years, the two year maximum applies under 37 C.F.R. § 1.775(d)(6)(ii)(B).

(13) Applicant, through its undersigned counsel, acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought, in accordance with 37 C.F.R. § 1.765.

(14) A check in the amount of $550, payable to the Commissioner of Patents and Trademarks is attached to cover the fee prescribed by 37 C.F.R. § 1.20(n) for receiving and acting upon this application for extension. The Commissioner is hereby authorized to charge any deficiency, or credit any surplus, in the amount indicated above relative to the required fee to our Account No. 03-3975, Order No. 59808.

(15) Please direct all inquiries and correspondence relating to this application for patent term extension to:

Donald J. Bird
Cushman Darby & Cushman
1615 L Street N.W., 11th Floor
Washington, D.C. 20036
(202) 861-3000

(16) Submitted herewith is a certification that these application papers are being submitted in duplicate.

(17) Additionally submitted herewith is a declaration signed by a duly authorized representative of the owner of record of the patent sought to be extended, in accordance with 37 C.F.R. § 1.740(a)(17) and (b).

Respectfully submitted,

CUSHMAN, DARBY & CUSHMAN

By: _____
Donald J. Bird
Reg. No. 25,323

CERTIFICATION

The undersigned hereby certifies that this Application For Extension of Patent Term Under 35 U.S.C. § 156, including THE EXHIBITS and supporting papers, is being submitted as duplicate originals.

February 22, 1988
Date

Donald J. Bird
Reg. No. 25,323